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ORIGINAL

Urinary creatinine excretion is related to short-term and long-term mortality in critically ill patients

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Abstract

Purpose: Patients with reduced muscle mass have a worse outcome, but muscle mass is difficult to quantify in the ICU. Urinary creatinine excretion (UCE) reflects muscle mass, but has not been studied in critically ill patients. We evaluated the relation of baseline UCE with short-term and long-term mortality in patients admitted to our ICU.

Methods: Patients who stayed ≥ 24 h in the ICU with UCE measured within 3 days of admission were included. We excluded patients who developed acute kidney injury stage 3 during the first week of ICU stay. As muscle mass is considerably higher in men than women, we used sex-stratified UCE quintiles. We assessed the relation of UCE with both in-hospital mortality and long-term mortality.

Results: From 37,283 patients, 6151 patients with 11,198 UCE measurements were included. Mean UCE was 54% higher in males compared to females. In-hospital mortality was 17%, while at 5-year follow-up, 1299 (25%) patients had died. After adjustment for age, sex, estimated glomerular filtration rate, body mass index, reason for admission and disease severity, patients in the lowest UCE quintile had an increased in-hospital mortality compared to the patients in the highest UCE quintile (OR 2.56, 95% CI 1.96–3.34). For long-term mortality, the highest risk was also observed for patients in the lowest UCE quintile (HR 2.32, 95% CI 1.89–2.85), independent of confounders.

Conclusions: In ICU patients without severe renal dysfunction, low urinary creatinine excretion is associated with short-term and long-term mortality, independent of age, sex, renal function and disease characteristics, underscoring the role of muscle mass as risk factor for mortality and UCE as relevant biomarker.

Keywords: Creatinine, Urinary creatinine excretion, Muscle mass, Muscle wasting, Sarcopenia, Glomerular filtration rate, In-hospital mortality, Long-term mortality

Introduction

Muscle mass is an important determinant of the ability of patients in the intensive care unit (ICU) to overcome their disease. Sarcopenia (i.e. loss of muscle and function) on ICU admission is an independent risk factor for morbidity and mortality in critically ill patients [1–3]. Although several physical and laboratory indicators of muscle mass have been used in various other patient groups [4, 5], muscle mass is difficult to quantify in ICU patients.

Creatinine is the stable end product of creatine. Most creatine is present in muscle and is converted at a steady rate to creatinine. Creatinine is released into the

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circulation and is almost exclusively excreted in the urine [6]. In steady state conditions, urinary excretion will equal creatinine production, irrespective of the serum creatinine concentration. Therefore, measurement of urinary creatinine excretion (UCE) in 24-h urine collections is a widely accepted method for muscle mass estimation in stable outpatient populations [5, 7–9]. In healthy subjects [10] and in patients with wasting conditions or (chronic) renal failure [4, 8], UCE has been associated with long-term mortality.

UCE has not been evaluated in critically ill patients. In our ICU, 24-h urine is routinely and continuously collected to measure UCE. We hypothesized that in critically ill patients baseline UCE, as a reflection of muscle mass, is related with mortality. We analyzed the relation of UCE with short-term and long-term mortality.

Take-home message:

Low urinary creatinine excretion early after ICU admission is a strong independent predictor of both short-term and long-term mortality, underscoring a role of muscle mass as risk factor for mortality. UCE thus constitutes a simple, readily available and relevant prognostic biomarker for critically ill patients.

Materials and methods

Study setting, patient selection and outcome

In this retrospective observational cohort study, we analyzed laboratory measurements of all patients aged 15 years and older who were admitted to our ICU in a university hospital between January 2002 and April 2016. Reason for ICU-admission, age, sex, height, weight and the acute physiology and chronic health evaluation score 4 (APACHE-IV) [11] were recorded. We routinely collect 24-h urine samples as part of standard care at our ICU to determine the measured creatinine clearance. From 00:00 to 24:00 all urine is collected in a large disposable container. Patients who were discharged within 24 h of ICU admission or for whom no 24-h urine samples were available in the first 3 days after admission (i.e. due to measurement errors in the lab or incomplete 24-h collections) were excluded. Only 24-h urine samples collected in the first 3 days after ICU admission were analyzed. UCE was determined by multiplying the urinary creatinine concentration in the 24-h urine with the 24-h urinary volume. We did not use weight-adjusted daily UCE, as we do not routinely weigh our patients. The median UCE was calculated for each patient and used for further analyses. Corresponding daily serum creatinine levels were also available. Acute kidney injury (AKI) was assessed for the first 7 days of ICU admission. Patients with acute kidney injury (AKI) stage 3 (i.e. increase of serum creatinine to > 300% from baseline, or ≥ 354 μmol/L (4 mg/dL) or requiring renal replacement therapy [12]) during the first 7 ICU days, were excluded because of their inability to produce urine or the unreliability of UCE as RRT interferes with UCE interpretation. Since complete data on urine output were often not available, we only used the serum creatinine based criteria of the KDIGO AKI guideline. We stratified for sex to account for the considerable difference in creatinine excretion resulting from differences in body weight and composition between men and women [13]. This study was approved by our hospital's medical ethical committee and since it concerned an analysis of anonymized laboratory and clinical data, all collected during standard clinical care, informed consent was not required (METc 2011/132).

Samples

Urinary and serum creatinine measurements were performed in the hospital's certified central laboratory. Serum creatine kinase activity (CK) measured at ICU day one was also recorded to assess a possible effect of rhabdomyolysis on creatinine. We did not exclude patients with potential rhabdomyolysis. Potential rhabdomyolysis was defined as CK ≥ 1500 U/L. Cardiothoracic surgery patients were not included in this subgroup. Estimated glomerular filtration (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [14] with serum creatinine, sex, and age as input variables. Body mass index (BMI) was calculated as weight (kg)/height^2 (m). In order to adjust for acute changes in renal clearance of creatinine we also calculated the estimated creatinine production, as described in the supplementary material file (SMF). Likewise, in the SMF we compared weight-adjusted UCE, i.e. UCE/kg with UCE in the predictive models in patients with available baseline body weight measurements.

Outcome

In-hospital mortality was used as the short-term outcome measure. We performed near-complete long-term follow-up to determine survival status in patients for 5 years after hospital discharge, as recorded in the hospital database and in the municipal mortality registry by January 2018.

Statistical analysis

Patient characteristics were calculated according to sex-stratified UCE quintiles. Data were expressed as mean and standard deviation (SD) when normally distributed or median and interquartile range (IQR) when skewed. A chi-square test for categorical variables and ANOVA for normally distributed continuous variables or a Kruskal–Wallis test for skewed distributed continuous variables was performed to determine variances between patient

characteristics across UCE quintiles. Missing data were imputed via multiple imputation (see SMF).

To assess associations of UCE with short-term and long-term mortality respectively, multivariable logistic regression and Cox proportional hazards regression analyses were performed. The proportional hazard assumption was verified by inspection of "log–log" plots and by introducing interactions with survival time. UCE was entered as a categorical variable (quintiles) and as a continuous variable (with OR/HR calculated per 5 mmol/24 h UCE decrease). Analyses were first performed in a crude model (model 1: adjusted for sex when UCE was entered as continuous variable). Further analyses cumulatively included adjustment for age (model 2), eGFR (model 3), BMI (model 4) and reason of admission and severity of illness (model 5). For patients discharged alive from the hospital, long-term survival was assessed with Kaplan–Meier survival curves according to the sex-stratified UCE quintiles and evaluated with the log-rank test. Patients who were lost to follow-up were censored at that particular time point. Splines were fit by a logistic regression model and a Cox proportional hazards regression model based on restricted cubic splines and adjustments as used in model 5. In secondary analyses, we tested for potential interaction by sex, age, BSA, renal function, disease severity and reason of admission. We also performed separate analyses for patients who developed AKI and for patients who did not develop AKI. Additional subgroup analyses were performed when effect modification was observed or when differences in UCE were expected in patient subgroups. In sensitivity analyses, we investigated for potential bias introduced by imputation, by restricting the dataset to complete cases. As additional sensitivity analysis, we assessed the potential confounding effect of rhabdomyolysis on UCE. Serum CK was log-transformed to adjust for its strongly skewed distribution. The secondary and sensitivity analyses as listed in the results and SMF were adjusted for potential confounders that were included in model 5. *P* values <0.05 were considered significant. Data were analyzed with SPSS 23.0 (IBM Inc. 2016, New York, USA) and *R*. version 3.4.2 (*R* foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and outcome

Of a total of 37,283 patients, 6151 patients were included. We excluded 28,493 patients because of ICU admission with a duration shorter than 24 h or incomplete 24-h urine collection. Another 2572 patients were excluded because of AKI stage 3 within 7 days of ICU admission, and finally 67 patients were excluded because of missing serum creatinine levels. In the remaining 6151 patients, a total of 11,198 24-h urine creatinine measurements (i.e. 1.8 measurements per patient) were determined during the first 3 ICU days (Fig. 1). The baseline clinical characteristics of the included patients are summarized in Table 1. Median age of the included patients was 62 (50–72) years and 62% were male. Median UCE (IQR) was 54% higher in men than women, i.e. 12.2 (9.0–15.7) vs. 7.9 (6.0–10.1) mmol/day ($P<0.001$). The mean UCE was similar on ICU-days 1 and 3 (10.8 ± 5.2 vs. 11.0 ± 5.1 mmol/day, $P=0.34$). Median urinary volume was 1.5 L (1.01–2.2). Reason for admission differed

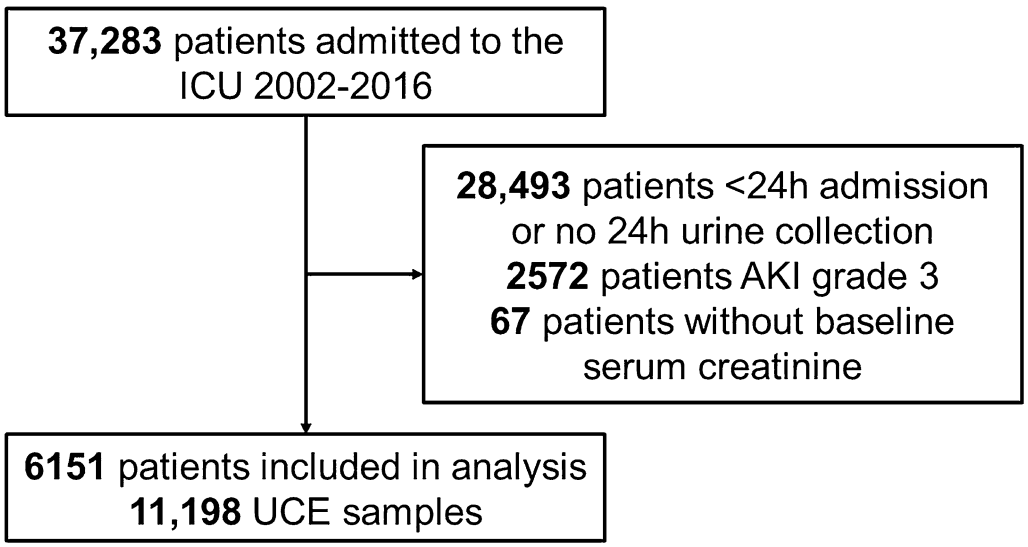

Fig. 1 Flowchart of patients included into the analysis

Table 1 Patient characteristics and outcome parameters

	UCE sex-stratified quintiles[a]					*P*
	Q1	*Q2*	*Q3*	*Q4*	*Q5*	
	♂ ≤ 8.25; ♀ ≤ 5.55	♂ > 8.25–10.9; ♀ > 5.55–7.10	♂ > 10.9–13.45; ♀ > 7.10–8.55	♂ > 13.45–16.65; ♀ > 8.55–10.50	♂ > 16.65; ♀ > 10.50	
Included patients	1228	1237	1208	1240	1238	
Male (%)	760 (62%)	770 (62%)	756 (63%)	764 (62%)	764 (62%)	0.987
Age, years	67 (56–76)	67 (58–76)	66 (56–73)	60 (48–69)	51 (38–61)	< 0.001
Urinary creatinine excretion, mmol/24 h	5.3 ± 2.0	8.4 ± 1.7	10.6 ± 2.2	12.9 ± 2.8	17.2 ± 4.5	< 0.001
Men	6.0 ± 1.9	9.7 ± 0.7	12.2 ± 0.7	15.0 ± 0.9	20.0 ± 3.1	< 0.001
Female	4.0 ± 1.3	6.3 ± 0.5	7.8 ± 0.4	9.5 ± 0.6	12.8 ± 2.4	< 0.001
Reason for admission (%)						< 0.001
Medical	173 (14%)	129 (10%)	126 (10%)	158 (13%)	153 (12%)	
Surgical						
Trauma	35 (3%)	48 (4%)	58 (5%)	117 (9%)	279 (23%)	
Abdominal/vascular	288 (23%)	297 (24%)	291 (24%)	315 (25%)	289 (23%)	
Transplantation	54 (4%)	66 (5%)	54 (4%)	51 (4%)	18 (2%)	
Neurosurgery	31 (3%)	32 (3%)	41 (3%)	59 (5%)	86 (7%)	
Cardiothoracic	243 (20%)	319 (26%)	347 (29%)	286 (23%)	193 (16%)	
Miscellaneous	408 (33%)	346 (28%)	291 (24%)	254 (21%)	220 (18%)	
ICU LOS, days	4.8 (2.6–10.1)	4.9 (2.7–10.1)	4.1 (2.3–8.7)	4.3 (2.3–9.6)	4.5 (2.5–9.8)	0.004
Hospital LOS, days	18.1 (9.2–34.7)	20.2 (12.1–34.2)	17.4 (11.2–30.0)	16.9 (10.3–28.2)	16.8 (10.2–28.7)	< 0.001
APACHE-IV[b]	73 ± 27	67 ± 24	64 ± 24	58 ± 24	53 ± 23	< 0.001
Length, cm[c]	171 ± 10	173 ± 9	174 ± 9	176 ± 9	178 ± 9	< 0.001
Weight, kg[d]	73 ± 16	75 ± 14	80 ± 15	83 ± 15	90 ± 18	< 0.001
BMI[c]	25 ± 5	25 ± 4	26 ± 4	27 ± 5	28 ± 6	< 0.001
BSA, m^{2} [c]	1.8 ± 0.2	1.9 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	< 0.001
Acute kidney injury	539 (44%)	414 (34%)	305 (25%)	233 (19%)	218 (18%)	< 0.001
Stage 1	353 (65%)	301 (73%)	229 (75%)	173 (79%)	163 (64%)	
Stage 2	186 (35%)	113 (27%)	76 (25%)	60 (27%)	55 (25%)	
Serum creatinine, µmol/L	86 (56–136)	76 (58–115)	73 (58–100)	70 (58–93)	69 (58–87)	< 0.001
eGFR (mL/min/1.73m2)	72 (40–102)	82 (51–100)	87 (61–101)	93 (69–107)	100 (81–114)	< 0.001

[a] Urinary creatinine excretion quintiles based on separate quintile intervals for males and females in mmol per day

[b] Data missing for 1709 (28%) patients

[c] Data missing for 1176 (19%) patients

[d] Data missing for 1173 (19%) patients

between the quintiles of UCE, with the highest number of trauma patients in the highest UCE quintile.

The median ICU length of stay was 4.6 (2.5–9.7) days, with a total hospital stay of 17.9 (10.8–30.7) days (Table 1). The median serum creatinine was 73 (57–104) µmol/L and 1709 patients (28%) developed AKI stage 1 or stage 2 in the first week of ICU stay. Serum creatinine decreased in the first 3 ICU days [day 1: 79 (62–104), day 3: 73 (57–106) µmol/L, $P < 0.001$]. Serum creatinine and incidence of AKI were inversely associated with UCE quintiles. Median eGFR was 92 (60–122) mL/min and was positively associated with UCE quintiles. Median follow-up time was 3.7 (2.1–7.6) years with a maximum of 16.1 years. A completeness of follow-up of 85% was achieved (see Supplementary Methods, SMF).

UCE and short-term mortality

Overall in-hospital mortality was 17%. In-hospital mortality decreased for the sex-specific quintiles of UCE, from 31% in the first quintile to 9% in the fifth quintile

Table 2 Logistic regression analyses of in-hospital mortality

	UCE[a]		UCE sex-stratified quintiles				
	(*n* = 6151)		Q1 (*n* = 1228)	Q2 (*n* = 1237)	Q3 (*n* = 1208)	Q4 (*n* = 1240)	Q5 (*n* = 1238)
	OR (95% CI)	*P*	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	Reference
Model 1[b]	1.81 (1.66–1.97)	< 0.001	4.34 (3.46–5.45)	2.24 (1.77–2.85)	1.58 (1.23–2.03)	1.32 (1.02–1.71)	1.00
Model 2[c]	1.67 (1.52–1.83)	< 0.001	3.32 (2.61–4.20)	1.69 (1.32–2.17)	1.22 (0.94–1.59)	1.14 (0.88–1.48)	1.00
Model 3[d]	1.65 (1.51–1.81)	< 0.001	3.21 (2.52–4.08)	1.68 (1.30–2.16)	1.24 (0.95–1.61)	1.15 (0.88–1.50)	1.00
Model 4[e]	1.70 (1.54–1.88)	< 0.001	3.47 (2.69–4.49)	1.80 (1.38–2.33)	1.30 (0.99–1.70)	1.19 (0.91–1.55)	1.00
Model 5[f]	1.49 (1.34–1.65)	< 0.001	2.56 (1.96–3.34)	1.45 (1.11–1.91)	1.09 (0.83–1.43)	1.08 (0.82–1.41)	1.00

Multivariable logistic regression to assess the association of UCE with in-hospital mortality

[a] UCE was entered as a continuous variable per 5 mmol/24 h decrease

[b] Model 1: adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles

[c] Model 2: adjusted as for model 1, additionally adjusted for age

[d] Model 3: adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD–EPI)

[e] Model 4: adjusted as for model 3, additionally adjusted for body mass index (BMI)

[f] Model 5: adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma)

($P < 0.001$, Fig. 2a). In multivariable logistic regression analyses with sex-specific quintiles of UCE, there was a 2.4 times increased risk of in-hospital mortality in the lowest sex-specific UCE quintile compared to highest quintile (OR 2.56, 95% CI 1.96–3.34, $P < 0.001$), independent of potential confounders (Table 2, model 5). In multivariable logistic regression analyses, with adjustment for sex, UCE expressed as a continuous variable was inversely associated with in-hospital mortality (for each 5 mmol/24 h decrease of UCE: OR 1.81, 95% CI 1.66–1.97, $P < 0.001$; Table 2). This association remained significant (OR 1.49, 95% CI 1.34–1.65, $P < 0.001$), independent of potential confounders (Table 2, model 5).

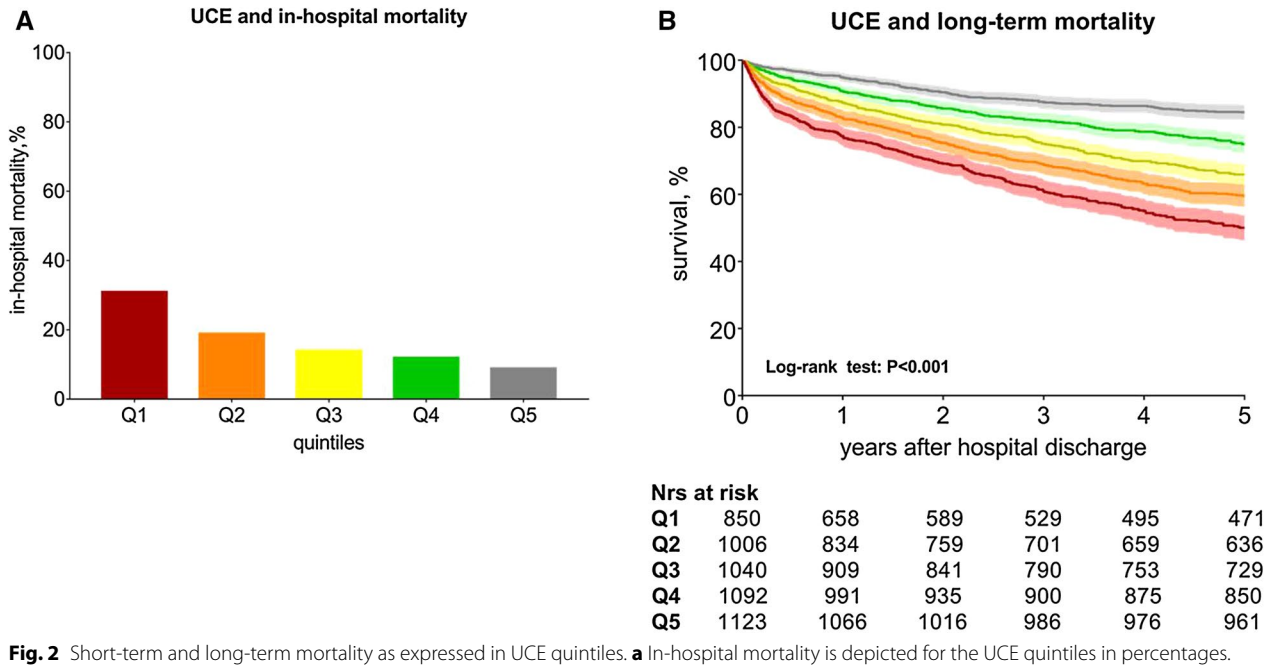

Fig. 2 Short-term and long-term mortality as expressed in UCE quintiles. **a** In-hospital mortality is depicted for the UCE quintiles in percentages. The first quintile represents the lowest UCE, the fifth quintile represents he highest quintile. Corresponding quintile cut-off values are shown in Table 1. In-hospital mortality increased when baseline UCE decreased (chi-square test: $P < 0.001$). **b** Kaplan–Meier curves for 5 year survival (with 95% CI) after hospital discharge. The colors of the quintiles correspond to colors as depicted in Fig. 2b. The highest UCE quintile had the best 5-year survival, which declined with declining baseline UCE (log-rank test: $P < 0.001$)

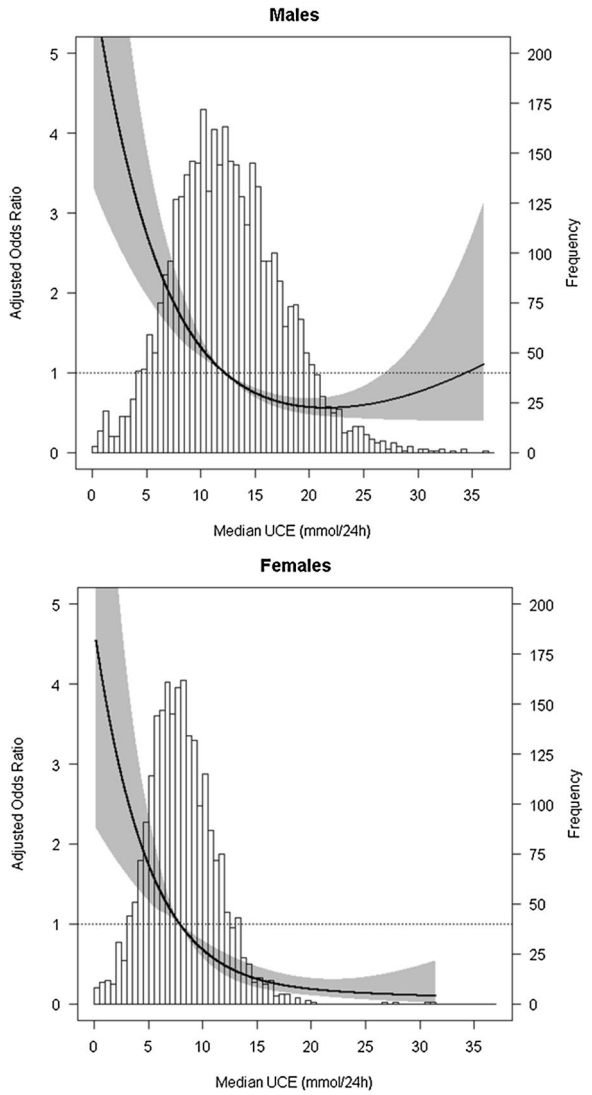

Fig. 3 Association between UCE and in-hospital mortality for both men and women. Data were fit by a multivariable logistic regression model based on restricted cubic splines. UCE was entered as continuous variable. Data were adjusted for sex, age, eGFR, BMI, severity of illness and reason of admission (model 5). Here, the median UCE was defined as the reference standard. The gray area represents the 95% CI. Here, the median UCE was defined as the reference standard. The curves in particular underscore the inverse relation of UCE with mortality for low and near median UCE values. Note the widely diverging 95% CI at the extremes resulting from the low patient numbers and the cubic fit

Because of the known sex difference in UCE, multivariable adjusted restricted cubic splines for the association of UCE with in-hospital mortality are shown separately for men and women in Fig. 3.

UCE and long-term mortality

For the 5111 patients who were discharged alive from the hospital, long-term mortality was assessed. Overall 5-year mortality was 29%. In univariate analysis, UCE showed a strong relation with long-term survival as illustrated by the Kaplan–Meier curves (log-rank test $P < 0.001$, Fig. 2b). In Cox-regression with UCE expressed in quintiles, patients in the lowest UCE quintile had a four times higher risk for long-term mortality compared to those in the highest UCE quintile (HR 4.03, 95% CI 3.35–4.84, $P < 0.001$, Table 3). After adjustment for potential confounders, this association remained independent (HR 2.32, 95% CI 1.89–2.85, $P < 0.001$, Table 3, model 5).

In Cox regression analysis with UCE expressed as a continuous variable, UCE was also associated with long-term mortality (HR 1.76, 95% CI 1.66–1.88 for each 5 mmol/d decrease of UCE, $P < 0.001$,Table 3). This association remained independent after adjustment for confounders with an HR of 1.49 (95% CI 1.38–1.62, $P < 0.001$, Table 3, model 5).

A multivariable adjusted restricted cubic spline for the association between UCE and mortality over 5 years for both men and women is shown in Fig. 4.

Subgroup, sensitivity and additional analyses

Additional subgroup and sensitivity analyses concerning the role of AKI, BMI and rhabdomyolysis amongst others, are presented and shown in the SMF (Tables ST1–ST10, Figures SF1–SF12). We found similar associations between UCE and short-term and long-term mortality in both the subgroup and sensitivity analyses. The association between UCE and short-term mortality was only not observed in trauma patients (OR 1.10, 95% CI 0.71–1.71, $P = 0.69$).

Discussion

This large prospective study shows that urinary creatinine excretion (UCE) early after ICU admission as a measure of muscle mass is strongly associated with both short-term and long-term mortality, independent of important covariates and confounders, including disease severity, age and renal function.

We consistently observed an inverse association between UCE and both short-term and long-term mortality, even in patients with chronic kidney disease or AKI (Tables ST1–ST10, Fig. SF4). Only for short-term outcome in trauma patients, no independent association with UCE was observed. However, a stronger association of UCE with long-term mortality was seen in the trauma patients when compared to the total patient group (Table ST4). As hospital mortality of severe trauma patients is mainly determined by age, severity of coma after trauma (and thus brain injury), base excess and

Table 3 Cox proportional hazard regression analyses for 5-year mortality

	UCE[a]		UCE sex-stratified quintiles				
	(*n* = 5111)		*Q1* (*n* = 850)	*Q2* (*n* = 1006)	*Q3* (*n* = 1040)	*Q4* (*n* = 1092)	*Q5* (*n* = 1123)
	HR (95% CI)	*P*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	Reference
Model 1[b]	1.76 (1.66–1.88)	< 0.001	4.03 (3.35–4.84)	3.02 (2.51–3.64)	2.36 (1.95–2.86)	1.65 (1.35–2.01)	1.00
Model 2[c]	1.56 (1.45–1.68)	< 0.001	2.58 (2.13–3.13)	1.88 (1.55–2.28)	1.53 (1.26–1.87)	1.25 (1.02–1.53)	1.00
Model 3[d]	1.56 (1.45–1.67)	< 0.001	2.59 (2.14–3.14)	1.87 (1.54–2.27)	1.52 (1.25–1.85)	1.24 (1.01–1.52)	1.00
Model 4[e]	1.56 (1.45–1.68)	< 0.001	2.59 (2.12–3.17)	1.87 (1.53–2.29)	1.52 (1.24–1.85)	1.24 (1.01–1.51)	1.00
Model 5[f]	1.49 (1.38–1.62)	< 0.001	2.32 (1.89–2.85)	1.71 (1.39–2.09)	1.39 (1.13–1.70)	1.17 (0.95–1.43)	1.00

Cox proportional hazard regression analysis to assess the association of UCE with 5-year survival

[a] UCE was entered as a continuous variable per 5 mmol/24 h decrease

[b] Model 1: adjusted for sex in continuous analyses, no adjustment for sex-adjusted quintiles

[c] Model 2: adjusted as for model 1, additionally adjusted for age

[d] Model 3: adjusted as for model 2, additionally adjusted for kidney function (eGFR CKD-EPI)

[e] Model 4: adjusted as for model 3, additionally adjusted for body mass index (BMI)

[f] Model 5: adjusted as for model 4, additionally adjusted for severity of illness (APACHE-IV) and reason of admission (trauma vs non-trauma)

coagulation disturbances [15], UCE is likely to be only a minor determinant of the short-term prognosis of trauma patients.

The relation of UCE with mortality has already been established in several other patient groups. A higher mortality in patients with low (baseline) UCE is present in renal transplant patients [16], patients with stroke [17], coronary artery disease [8], heart failure [18] and chronic kidney disease [19]. Moreover, a similar association is observed in the general population [10]. We are the first to examine the relationship of UCE with mortality in a large heterogenic critically ill patient group.

In several ICU subgroups, a J-shaped association between BMI and mortality was shown [20]. Other studies also show a beneficial effect of a moderately elevated BMI in several patient groups, including the critically ill [21–26]. It is very plausible that the increased mortality of patients with a low BMI results from the adverse effects of sarcopenia, as we found the highest mortality risk in patients in the lowest UCE quintile after adjustment for BMI (Table ST6).

In patients without AKI, a decreased serum creatinine also is a reflection of muscle wasting [27] and two large studies showed that low baseline serum creatinine is an independent risk factor for mortality [27, 28]. Changes in serum creatinine, i.e. in AKI patients, seem only to be associated with short-term mortality [29]. Prognostic ICU-models often incorporate serum creatinine as a measure of renal function [11, 30]. Although the APACHE-IV score also considers a lowered serum creatinine level (< 53 μmol L^{-1} or < 0.6 mg dL^{-1}) a mortality risk [11], no prognostic ICU-scoring system utilizes UCE as an outcome predictor. Both serum creatinine and UCE are influenced by renal insufficiency, but in steady-state conditions, urinary excretion will equal creatinine production, irrespective of the serum creatinine concentration. UCE will, therefore, better reflect muscle mass than serum creatinine, especially in patients with renal insufficiency. UCE determined early after ICU-admission might, therefore, improve prognostic ICU models and could be a significant contribution to the evolution of prognostic scores.

In our study we focused on UCE within 3 days of ICU admission and we did not focus on subsequent changes during ICU admission. In a recent study a decrease in UCE was seen after 7 and 14 days of ICU treatment, reflecting the gradual loss of muscle during ICU stay [31]. It seems plausible that a progressive decrease in UCE would further predict poor outcome, but this has to be assessed in future studies.

Although UCE presents a non-invasive and inexpensive method in ICU-patients, other methods of muscle mass estimation have been well researched in several patient populations; most are poorly suited for ICU patients [32–37]. In the critically ill patient, anthropometric measurements such as body weight, BMI, waist circumference or mid-arm or mid-thigh muscle area are often complicated by the presence of dehydration, ascites or edema. More advanced techniques such as computed tomography, magnetic resonance imaging or dual-energy X-ray absorptiometry are both expensive and impractical for routine use in the ICU [5]. Bioelectrical impedance analysis is a simple and non-invasive method that is widely used to obtain estimates of body composition [38], but its accuracy in detecting loss of muscle mass in ICU patients is questionable because its measurement requires fluid

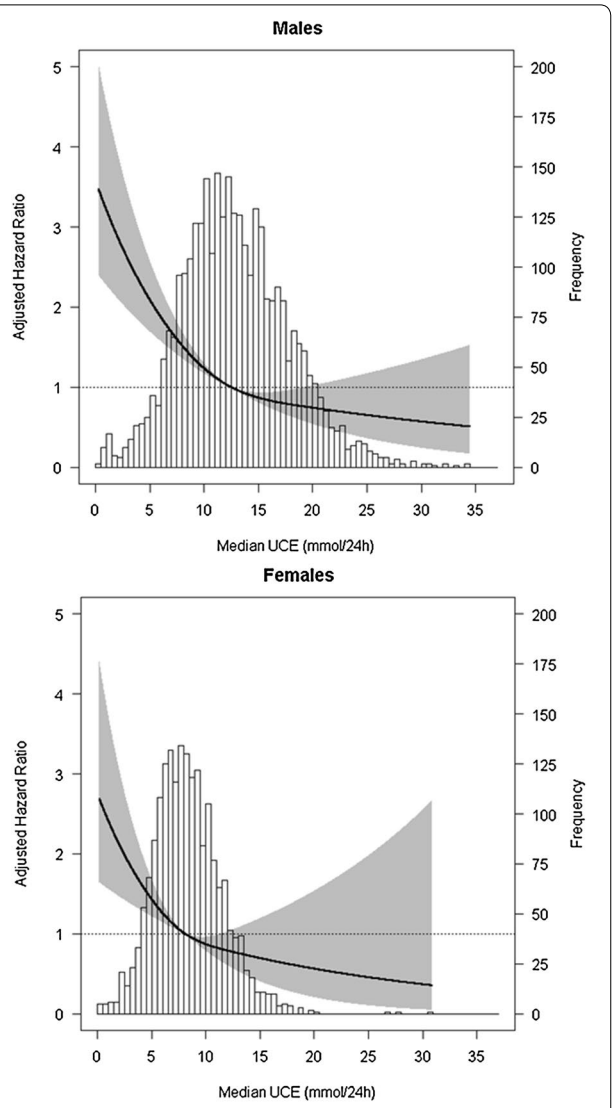

Fig. 4 Association between UCE and 5-year survival for both men and women discharged alive. Data were fit by a Cox proportional hazard regression model based on restricted cubic splines. UCE was entered as continuous variable. Data were adjusted for sex, age, eGFR, BMI, severity of illness and reason of admission (model 5). The gray area represents the 95% CI

homeostasis [39]. Repeated ultrasonography for the detection of muscle wasting shows promising results in a few relatively small studies [33–35], but muscle dimensions are also influenced by generalized edema. In this regard, it would be interesting to compare UCE with both bioelectrical impedance and ultrasonography in a larger study population, while taking the fluid balance into account.

Some limitations of our study are due to its post hoc design and the long period it covers. An important potential limitation of UCE are the rapid changes in glomerular filtration rate as are common in the critically ill [40, 41]. UCE may decrease in patients with acute kidney injury, who have a higher risk of dying [30]. In some cases, UCE may increase because of augmented renal clearance, as has been reported in some younger trauma and sepsis patients [40]. Also, glomerular filtration may be altered by commonly administered drugs, such as vasopressors and diuretics [42, 43]. The differences in mortality could thus possibly be attributed to other factors such as renal function or hypercatabolism instead of muscle mass. We were unfortunately not able to address this as we did not perform true GFR measurements or other muscle mass measurements.

The relevance of decreased or increased glomerular filtration or creatinine clearance with respect to UCE could best be addressed by determining this parameter as well. We did adjust for eGFR as potential confounder; however, in the case of AKI it may take time before serum creatinine rises, limiting the value of this adjustment. However, mean UCE did not significantly differ between days 1 and 3, and we excluded patients with severe AKI (stage 3). Furthermore, separate analyses performed for both patients without and with AKI stage 1 or 2 (SMF: Table ST3a, ST3b, Fig. SF4) led to similar findings. Finally, we excluded patients with AKI stage 3, also because UCE cannot be determined in anuric patients. This is an obvious limitation of using this marker as a prognostic score. Estimation of muscle mass by measurement of UCE also requires complete 24 h urine collection by ICU-nurses. Since ICU patients typically have indwelling urine catheters, this was an advantage in our population. In non-ICU patients who often have to collect the 24-h urine themselves, it is therefore considered a less reliable method [4]. Creatinine levels in patients who are on an oral diet may also be increased by meat intake. In our study, this potential confounding factor was of no influence since all patients were on enteral or parenteral feeding containing no dietary meat. Our population consists of predominantly surgical rather than medical ICU patients. However, we saw similar findings in the population of non-surgical ICU patients (See SMF) and UCE was found to be a strong predictor of mortality in non-ICU medical patients as well [10, 17–19]. Recently, the sarcopenia index has been proposed as a measure for muscle mass [36, 37]. Although promising, we were unable to use this index as it requires cystatine C measurement. Due to the retrospective nature of our study we were not able to compare UCE with other methods that estimate muscle mass, i.e. the paraspinal muscle surface area at lumbal vertebral levels measured on CT [5, 37]. However, future studies could assess the relationship between UCE and other muscle mass measures.

In conclusion, low urinary creatinine excretion early after ICU admission is a strong independent predictor of both short-term and long-term mortality after adjustment for BMI, renal function and severity of disease, underscoring a role of muscle mass as risk factor for mortality. UCE thus constitutes a simple, readily available and relevant prognostic biomarker for critically ill patients.

Electronic supplementary material
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